

**Example 32**

**Compound 84** (Scheme 13). To a solution of naproxen **1** (1.15g, 5 mmol) and 5 2-(methylthio)ethanol **80** (0.46g, 5 mmol) and 4-(dimethylamino)pyridine (DMAP) (0.12g, 1 mmol) in 50 ml of  $\text{CH}_2\text{Cl}_2$  was added DCC (1.03g, 5 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 2 h. The solid was filtered off and the solvent was evaporated. The residue was partially dissolved in EtOAc and the mixture was filtered to remove more solid. The filtrate was washed with water (50 x 2), dried 10 ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Recrystallization of the crude product from hexanes provided 0.96g of the compound **84** as a white crystal;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.59 (d, 3H), 2.05 (s, 3H), 2.65 (m, 2H), 3.86 (q, 1H), 3.91 (s, 3H), 4.25 (m, 2H), 7.11-7.25 (m, 2H), 7.41 (d, 1H), 7.67-7.71 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  15.9, 16.8, 32.6, 45.6, 55.5, 63.7, 105.8, 119.2, 126.2, 126.4, 127.4, 129.1, 129.4, 133.9, 135.7, 157.9, 174.7; 15 MS (ESI)  $m/z$  327.4 ( $\text{M} + \text{Na}^+$ ) ( $\text{C}_{17}\text{H}_{20}\text{O}_3\text{SNa}$  requires 327.1).

**Compound 50** (Scheme 13). To a solution of compound **84** (0.09g, 0.3 mmol) in 3 ml of acetone was added *m*-chloroperoxybenzoic acid (*m*-CPBA) (0.25g, 1.5 mmol). The resulting solution was stirred at 0 °C for 3 h. A solution of  $\text{Na}_2\text{SO}_3$  was 20 added to quench the reaction and then more water was added. The resulted mixture was filtered and washed with methanol to give a compound which has the identical  $^1\text{H}$  NMR and MS properties to compound **50** produced by the procedure set forth in Example 17 above.

**Example 33**

**Compound 85** (Scheme 13). Compound **85** was prepared by the similar procedure as described above for compound **84** from naproxen **1** (6.9g, 30 mmol), methylthiopropanol **81** (3.06 ml, 3.18g, 30 mmol), DMAP (0.72g, 6 mmol) and DCC (6.18g, 30 mmol). The compound was purified by recrystallization from hexanes to 30 give 6.7g (70%) of the compound **85** as a white crystal;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.58 (d, 3H), 1.85 (m, 2H), 1.97 (s, 3H), 2.39 (t, 2H), 3.85 (q, 1H), 3.91 (s, 3H), 4.17 (m, 2H),

7.11-7.15 (m, 2H), 7.39-7.41 (m, 1H), 7.66-7.71 (m, 3H); MS (ESI) *m/z* 441.5 (M + Na)<sup>+</sup>. (C<sub>18</sub>H<sub>22</sub>O<sub>3</sub>SNa requires 441.2).

**Compound 88** (Scheme 13). Compound 88 was prepared by the similar procedure as described above for compound 50 from compound 85 (1.27g, 4 mmol) and *m*-CPBA (3.4g, 20 mmol). The product was purified by recrystallization from EtOAc-hexanes to give 1.1g (80%) of the compound 88 as a white powder; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.58 (d, 3H), 2.08 (m, 2H), 2.59 (s, 3H), 2.75 (m, 2H), 3.86 (q, 1H), 3.91 (s, 3H), 4.16 (m, 1H), 4.26 (m, 1H), 7.11-7.16 (m, 2H), 7.37-7.39 (m, 1H), 7.66 (s, 1H), 7.70-7.73 (m, 2H); MS (ESI) *m/z* 373.3 (M + Na)<sup>+</sup> (C<sub>18</sub>H<sub>22</sub>O<sub>3</sub>SNa requires 373.1).

#### Example 34

**Compound 86** (Scheme 13). Compound 86 was prepared by the similar procedure as described above for compound 84 from naproxen 1 (6.9g, 30 mmol), methylthiobutanol 82 (3.6g, 30 mmol), DCC (6.18g, 30 mmol) and DMAP (0.72g, 6 mmol). The product was purified by recrystallization from hexanes to give 7.3g (73%) of the compound 86 as a white solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.54 (m, 2H), 1.58 (d, 3H), 1.67 (m, 2H), 1.96 (s, 3H), 2.40 (t, 2H), 3.85 (q, 1H), 3.89 (s, 3H), 4.09 (t, 2H), 7.10-7.15 (m, 2H), 7.39-7.41 (q, 1H), 7.66-7.70 (t, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 15.35, 18.59, 25.48, 27.74, 33.72, 45.61, 55.3, 64.37, 105.70, 119.08, 126.02, 126.32, 127.24, 129.04, 129.37, 133.80, 135.85, 157.74, 174.76; MS (ESI) *m/z* 355.3 (M + Na)<sup>+</sup> (C<sub>19</sub>H<sub>24</sub>O<sub>3</sub>SNa requires 355.1).

**Compound 89** (Scheme 13). Compound 89 was prepared by the similar procedure as described above for compound 50 from compound 86 (1.33g, 4 mmol), *m*-CPBA (3.5g, 20 mmol) in 35 ml of acetone. The product was purified by recrystallization from CH<sub>2</sub>Cl<sub>2</sub>-hexane to give 1.13g (78%) of the compound 89 as a pale yellow solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.57 (d, 3H), 1.73 (m, 4H), 2.56 (s, 3H), 2.82 (m, 2H), 3.65 (q, 1H), 3.90 (s, 3H), 4.08 (m, 1H), 4.15 (m, 1H), 7.10-7.15 (m, 2H), 7.38-7.40 (q, 1H), 7.65 (s, 1H), 7.70 (d, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 18.5, 19.4, 27.5,

40.2, 45.6, 54.2, 55.5, 63.7, 105.8, 119.4, 126.1, 126.3, 127.4, 129.1, 129.4, 133.9, 135.8, 157.9, 174.7; MS (ESI)  $m/z$  387.5 ( $M + Na$ )<sup>+</sup> ( $C_{19}H_{24}O_5SNa$  requires 387.5).

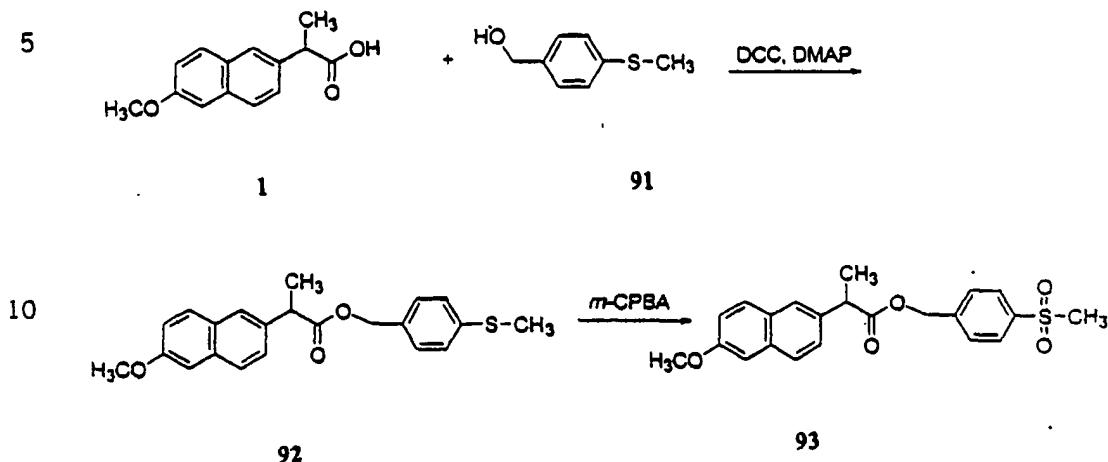
### Example 35

5       **Compound 87** (Scheme 13). Compound 87 was prepared by the similar procedure as described above for compound 84 from naproxen 1 (1.15g, 5 mmol), 2-(phenylthio)ethanol 83 (0.77g, 5 mmol), DCC (1.03g, 5 mmol) and DMAP (0.12g, 1 mmol) in 50 ml of  $CH_2Cl_2$ . The product was purified by recrystallization from hexanes to give 1.0g (56%) of the compound 87 as a white powder;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.56 (d, 3H), 3.10 (m, 2H), 3.83 (q, 1H), 3.91 (s, 3H), 4.25 (m, 2H), 7.11-7.40 (m, 8H), 7.65-7.70 (m, 3H);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  18.7, 32.5, 45.6, 55.5, 63.4, 105.8, 119.2, 126.2, 126.4, 126.8, 127.4, 129.1, 129.2, 129.5, 130.1, 133.9, 135.3, 135.7, 157.9, 174.7; MS (ESI)  $m/z$  389.5 ( $M + Na$ )<sup>+</sup> ( $C_{22}H_{22}O_2SNa$  requires 389.2).

15       **Compound 90** (Scheme 13). Compound 90 was prepared by the similar procedure as described above for compound 50 from compound 87 (1.46g, 4 mmol), *m*-CPBA (3.5g, 20 mmol) in 35 ml of acetone. The product was purified by recrystallization from  $CH_2Cl_2$ -hexane to give 1.2g (75%) of the compound 90 as a white solid;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.46 (d, 3H), 3.40 (m, 2H), 3.59 (q, 1H), 3.92 (s, 3H), 4.33 (m, 1H), 4.45 (m, 1H), 7.11-7.85 (m, 11H);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  18.6, 45.2, 55.2, 55.5, 58.1, 105.8, 119.3, 126.2, 127.4, 128.3, 129.1, 129.4, 129.5, 133.9, 134.1, 135.1, 139.5, 158.0, 174.2; MS (ESI)  $m/z$  399.4 ( $M + H$ )<sup>+</sup> ( $C_{22}H_{23}O_5S$  requires 399.5)

The synthesis described in Example 36 is outlined in Scheme 14.

**Scheme 14**



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### Example 36

**Compound 92 (Scheme 14).** Compound 92 was prepared by the similar procedure as described above for compound 84 from methylthiobenzene alcohol 91 (4.6g, 30 mmol), naproxen 1 (6.9g, 30 mmol), DCC (6.18g, 30 mmol) and DMAP (0.72g, 6 mmol). The product was purified by recrystallization from  $\text{CH}_2\text{Cl}_2$ -hexanes to give 8.6g (78%) of the compound 92 as a white crystal;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.58 (d, 3H), 2.45 (s, 3H), 3.89 (q, 1H), 3.92 (s, 3H), 5.05 (q, 2H), 7.11-7.16 (m, 6H), 7.37-7.39 (m, 1H), 7.63-7.70 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  15.9, 18.7, 45.7, 55.5, 66.3, 105.8, 119.2, 126.2, 126.5, 126.7, 127.3, 128.9, 129.1, 129.5, 132.9, 133.9, 135.7, 138.8, 157.9, 174.6; MS (ESI)  $m/z$  389.4 ( $\text{M} + \text{Na}$ )<sup>+</sup> ( $\text{C}_{22}\text{H}_{32}\text{O}_3\text{Sna}$  requires 389.5)

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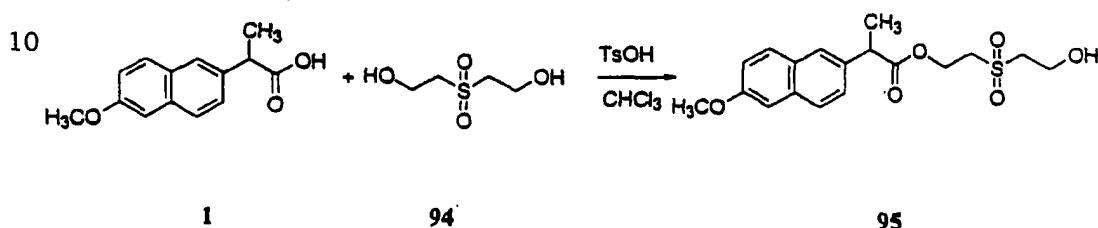
**Compound 93** (Scheme 14). Compound 93 was prepared by the similar procedure as described above for compound 50 from compound 92 (1.1g, 3 mmol), *m*-CPBA (1.34g, 7.5 mmol) in 30 ml of acetone. The product was purified by flash chromatography on a silica gel column using  $\text{CH}_2\text{Cl}_2$  as an eluent to give 1.0g (85%) of the compound 93 as a white solid;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.61 (d, 3H), 2.99 (s, 3H),

3.92 (s, 3H), 3.93 (q, 1H), 5.18 (q, 2H), 7.12-7.16 (m, 2H), 7.34-7.39 (m, 3H), 7.65-7.71 (m, 3H), 7.81 (d, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  18.5, 44.7, 45.6, 55.5, 65.3, 105.8, 119.4, 126.2, 126.3, 127.5, 127.8, 128.3, 129.1, 129.4, 133.9, 135.3, 140.2, 142.5, 158.0, 174.4; MS (ESI)  $m/z$  398.9  $\text{M}^+$  ( $\text{C}_{22}\text{H}_{30}\text{O}_5\text{S}$  requires 398.5)

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The synthesis described in Example 37 is outlined in Scheme 15.

**Scheme 15**



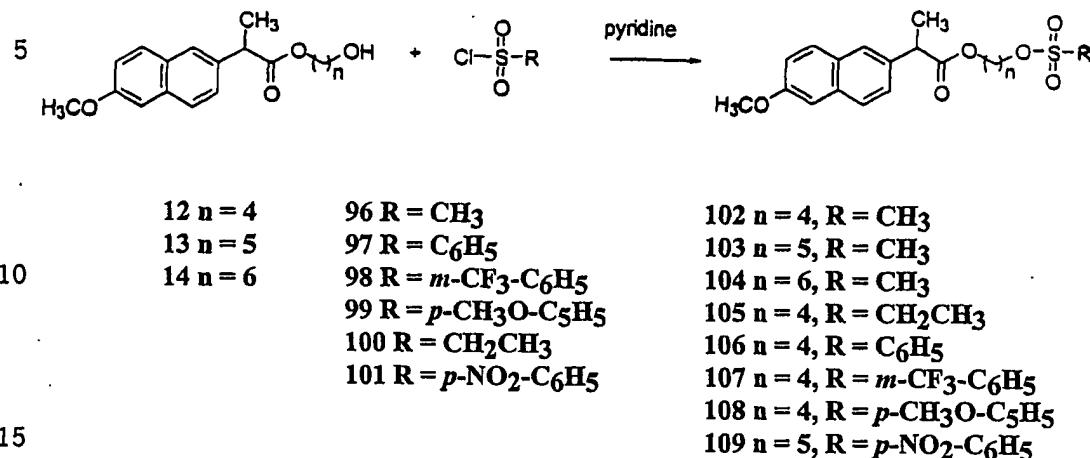
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### Example 37

**Compound 95** (Scheme 15). A mixture of 2, 2'-sulfonyldiethanol **94** (12.5 ml, 60% in H<sub>2</sub>O, 9.25g, 60 mmol) and CHCl<sub>3</sub> was heated to reflux to remove the water and then naproxen **1** (4.6g, 20 mmol) and 4-toluenesulfonic acid (TsOH) (0.25g, 1.3 mmol) were added to the above mixture. The resulting mixture was continued to reflux for 6 h. The reaction mixture was washed with water twice, 10% Na<sub>2</sub>CO<sub>3</sub> solution twice and then water once. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent was evaporated. The crude product was recrystallized from CHCl<sub>3</sub>-hexanes to give 0.41g of the compound **95** as a white powder; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.60 (d, 3H), 1.85 (bs, 1H, ex D<sub>2</sub>O), 2.51-2.56 (m, 1H), 2.62-2.67 (m, 1H), 3.25-3.28 (m, 2H), 3.48-3.51 (m, 2H), 3.88 (q, 1H), 3.92 (s, 3H), 4.41-4.46 (m, 1H), 4.56-4.61 (m, 1H), 7.11 (d, 1H), 7.15-7.18 (q, 1H), 7.35-7.36 (q, 1H), 7.65 (s, 1H), 7.69-7.74 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 18.3, 45.6, 54.0, 55.5, 55.6, 56.2, 56.3, 58.6, 105.8, 119.8, 126.1, 126.4, 127.7, 129.0, 133.9, 135.2, 158.2, 173.9; MS (ESI) *m/z* 389.1 (M + Na)<sup>+</sup> (C<sub>18</sub>H<sub>22</sub>O<sub>6</sub>Sna requires 389.1)

The syntheses described in Examples 38-45 are outlined in Scheme 16.

**Scheme 16**



**Example 38**

**Compound 102** (Scheme 16). A solution of compound **12** (3.02g, 10 mmol) and methansulfonyl chloride **96** (1.55 ml, 2.29g, 20 mmol) in 10 ml of pyridine was stirred at 0 °C for 2 h. 100 ml of water was added and the resulting mixture was filtered and the solid was washed with water five times. The compound was purified by rerecrystallization from CH<sub>2</sub>Cl<sub>2</sub>-hexanes to give 3.0g (79%) of the compound **102** as a white solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.58 (d, 3H), 1.67 (m, 4H), 2.88 (s, 3H), 3.85 (q, 1H), 3.91 (s, 3H), 4.10 (m, 4H), 7.11-7.15 (m, 2H), 7.38-7.40 (q, 1H), 7.65-7.71 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 18.6, 24.9, 25.9, 37.5, 45.6, 55.5, 63.9, 69.4, 105.8, 119.2, 126.1, 126.4, 127.4, 129.1, 129.4, 133.9, 136.8, 157.9, 174.8; MS (ESI) m/z 403.6 (M + Na)<sup>+</sup> (C<sub>19</sub>H<sub>24</sub>O<sub>6</sub>Sna requires 403.5).

**Example 39**

**Compound 103** (Scheme 16). Compound **103** was prepared by the similar procedure as described above for compound **102** from compound **13** (4.74g, 15 mmol)

and compound **96** (2.31 ml, 3.43g, 30 mmol). The product was purified by recrystallization from  $\text{CH}_2\text{Cl}_2$ -hexanes to give 5.1g (86%) of the compound **103** as a white solid;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.30 (m, 2H), 1.58 (d, 3H), 1.62 (m, 4H), 2.9 (s, 3H), 3.89 (q, 1H), 3.91 (s, 3H), 4.02-4.11 (m, 4H), 7.11-7.15 (m, 2H), 7.39 (d, 1H), 7.66-7.71 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  18.5, 22.1, 28.1, 28.8, 37.4, 45.7, 55.5, 64.5, 69.8, 105.8, 119.2, 126.1, 126.4, 127.3, 129.4, 133.9, 135.9, 157.9, 174.9; MS (ESI)  $m/z$  395.1 ( $\text{M} + \text{H}$ ) $^+$  ( $\text{C}_{20}\text{H}_{27}\text{O}_6\text{S}$  requires 395.1).

#### Example 40

10 **Compound 104** (Scheme 16). Compound **104** was prepared by the similar procedure as described above for compound **102** from compound **14** (3.3g, 10 mmol) and compound **96** (1.55 ml, 2.31g, 20 mmol). The product was purified by recrystallization from  $\text{CH}_2\text{Cl}_2$ -hexanes to give 1.72g (42%) of the compound **104** as a white solid;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.21-1.31 (m, 4H), 1.53-1.61 (m, 7H), 2.95 (s, 3H), 3.89 (q, 1H), 3.91 (s, 3H), 4.04-4.12 (m, 4H), 7.12-7.15 (m, 2H), 7.40 (q, 1H), 7.69 (t, 3H); MS (ESI)  $m/z$  431.4 ( $\text{M} + \text{Na}$ ) $^+$  ( $\text{C}_{21}\text{H}_{28}\text{O}_6\text{Sna}$  requires 431.5).

#### Example 41

20 **Compound 105** (Scheme 16). Compound **105** was prepared by the similar procedure as described above for compound **103** from compound **12** (1.51g, 5 mmol) and compound **100** (0.94 ml, 1.28g, 10 mmol). The product was purified by flash chromatography on a silica gel column using  $\text{CH}_2\text{Cl}_2$  as an eluent to give 1.45g (74%) of the compound **105** as a pale yellow oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.35 (t, 3H), 1.57 (d, 3H), 1.68 (m, 4H), 3.01 (q, 2H), 3.84 (q, 1H), 3.90 (s, 3H), 4.11 (m, 4H); MS (ESI)  $m/z$  417.4 ( $\text{M} + \text{Na}$ ) $^+$  ( $\text{C}_{20}\text{H}_{26}\text{O}_6\text{Sna}$  requires 417.5).

#### Example 42

20 **Compound 106** (Scheme 16). Compound **106** was prepared by the similar procedure as described above for compound **102** from compound **12** (1.51g, 5 mmol) and compound **97** (1.27 ml, 1.76 g, 10 mmol). The product was washed with water

and dried to give 1.9g (86%) of the compound **106** as a pale yellow oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.53 (d, 3H), 1.55-1.63 (m, 4H), 3.81 (q, 1H), 3.91 (s, 3H), 3.94-4.03 (m, 4H), 7.11-7.15 (m, 2H), 7.36 (d, 1H), 7.51 (m, 2H), 7.63 (m, 2H), 7.69 (d, 2H), 7.85 (d, 2H); MS (ESI) *m/z* 443.6 (M + H)<sup>+</sup> (C<sub>24</sub>H<sub>27</sub>O<sub>6</sub>S requires 443.5).

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#### Example 43

**Compound 107** (Scheme 16). Compound **107** was prepared by the similar procedure as described above for compound **102** from compound **12** (1.51g, 5 mmol) and compound **98** (1.55 ml, 2.45g, 10 mmol). The product was purified by flash chromatography on a silica gel column using CH<sub>2</sub>Cl<sub>2</sub> as an eluent to give 1.12g (44%) of the compound **107** as a white solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.56 (d, 3H), 1.60-1.63 (m, 4H), 3.82 (q, 1H), 3.90 (s, 3H), 4.00-4.06 (m, 4H), 7.11-7.15 (m, 2H), 7.36-7.38 (q, 1H), 7.64-7.71 (m, 4H), 7.89 (d, 1H), 8.04 (d, 1H), 8.15 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 18.5, 24.8, 25.7, 45.6, 55.5, 63.7, 70.8, 105.8, 119.2, 125.06, 125.09, 126.3, 127.4, 129.1, 129.4, 130.3, 130.6, 131.2, 132.1, 133.9, 135.8, 137.6, 157.9, 174.8; MS (ESI) *m/z* 533.3 (M + Na)<sup>+</sup> (C<sub>25</sub>H<sub>25</sub>F<sub>3</sub>O<sub>6</sub>Sna requires 533.5).

#### Example 44

**Compound 108** (Scheme 16). Compound **108** was prepared by the similar procedure as described above for compound **102** from compound **12** (1.51g, 5 mmol) and compound **99** (2.06g, 10 mmol). The product was purified by recrystallization from CH<sub>2</sub>Cl<sub>2</sub>-hexanes to give 1.44g (61%) of compound **108** as a white crystal; <sup>1</sup>H NMR and MS spectra are consistence with the compound **108**.

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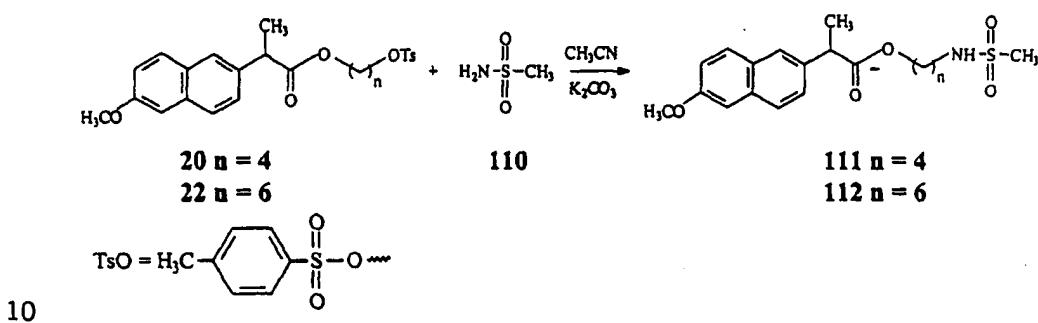
#### Example 45

**Compound 109** (Scheme 16). Compound **109** was prepared by the similar procedure as described above for compound **102** from compound **13** (1.58g, 5 mmol) and compound **101** (2.21g, 10 mmol). The product was purified by flash chromatography on a silica gel column using CH<sub>2</sub>Cl<sub>2</sub> as an eluent to give 1.5g (67%) of the compound **109** as a pale yellow oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.21-1.26 (m, 2H),

1.50-1.59 (m, 7H), 3.83 (q, 1H), 3.91 (s, 3H), 3.89-4.08 (m, 4H), 7.11-7.26 (m, 2H), 7.37-7.40 (m, 1H), 7.63-7.70 (m, 3H), 8.02 (d, 2H), 8.35 (d, 2H); MS (ESI) *m/z* 524.6 ( $M + Na$ )<sup>+</sup> ( $C_{25}H_{27}NO_8SNa$  requires 524.6).

5 The syntheses described in Examples 46 and 47 are outlined in Scheme 17.

**Scheme 17**



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**Example 46**

Compound 111 (Scheme 17). A mixture of compound 20 (4.56g, 10 mmol), methanesulfonamide 110 (1.9g, 20 mmol, 2 equiv) and  $K_2CO_3$  (6.9g, 50 mmol, 5 equiv) in 100 ml of acetonitrile ( $CH_3CN$ ) was heated to reflux for 26 h. The solvent was evaporated and the residue was dissolved and shaken well in water and  $EtOAc$ . The two phases were separated and the organic phase was washed with water three times, dried ( $Na_2SO_4$ ) and concentrated. The crude product was purified by recrystallization from  $CH_2Cl_2$ -hexanes to give 2.53g (67%) of the compound 111 as an 15 yellow solid;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.38-1.42 (m, 2H), 1.53-1.63 (m, 2H), 1.58 (d, 3H), 2.77 (s, 3H), 2.92-2.96 (m, 2H), 3.85 (q, 1H), 3.91 (s, 3H), 3.99 (bs, 1H, ex  $D_2O$ ), 20 4.03-4.07 (m, 1H), 4.11-4.16 (m, 1H), 7.12-7.16 (m, 2H), 7.38-7.40 (d, 1H), 7.66 (s, 1H), 7.71 (d, 2H); MS (ESI) *m/z* 402.5 ( $M + Na$ )<sup>+</sup> ( $C_{19}H_{25}NO_5SNa$  requires 402.5).

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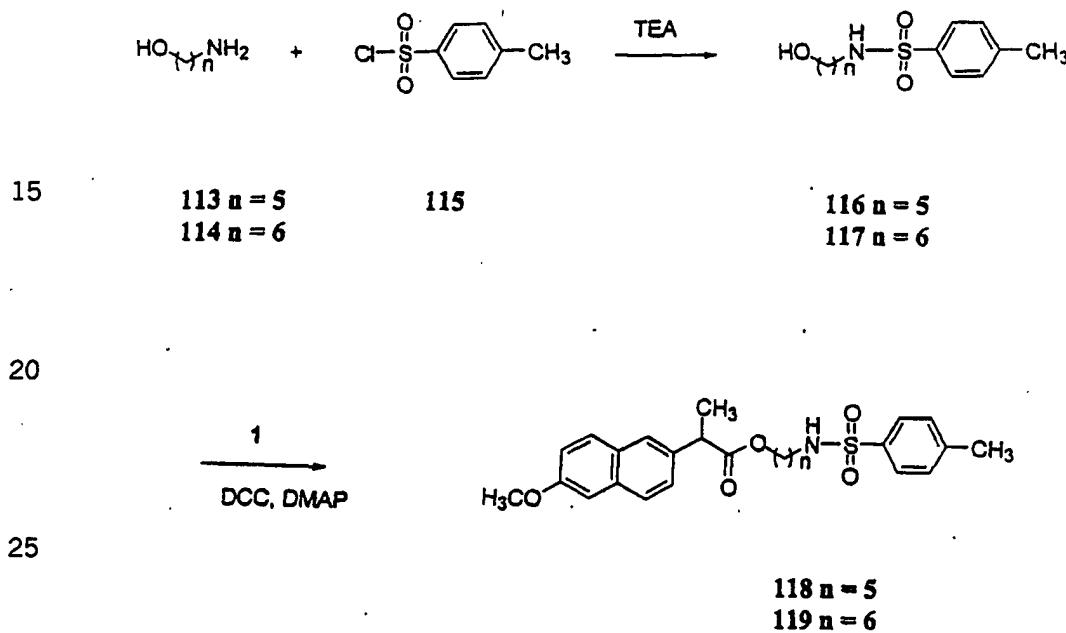
**Example 47**

Compound 112 (Scheme 17). Compound 112 was prepared by the similar procedure as described above for compound 111 from compound 22 (2.42g, 5 mmol) and compound 110 (0.57g, 6 mmol, 1.2 equiv). The product was purified by

recrystallization from  $\text{CH}_2\text{Cl}_2$ -hexanes to give 0.9g (45%) of the compound 112 as a powder;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.17-1.22 (m, 4H), 1.33-1.37 (m, 2H), 1.56 (d, 3H), 1.52-1.60 (m, 2H), 2.89 (s, 3H), 2.95 (q, 2H), 3.85 (q, 1H), 3.91 (s, 3H), 4.01-4.15 (m, 3H, 1H ex  $\text{D}_2\text{O}$ ), 7.12-7.15 (m, 2H), 7.40 (d, 1H), 7.66-7.76 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  18.5, 25.5, 26.1, 28.5, 30.1, 40.5, 43.2, 45.7, 55.5, 64.6, 105.8, 119.2, 126.1, 126.5, 127.3, 129.1, 129.4, 133.9, 136.1, 157.8, 174.9; MS (ESI)  $m/z$  430.6 ( $\text{M} + \text{Na}$ ) $^+$  ( $\text{C}_{21}\text{H}_{29}\text{NO}_5\text{Sna}$  requires 430.6).

The syntheses described in Examples 48 and 49 are outlined in Scheme 18.

10 **Scheme 18**



### Example 48

30 **Compound 116** (Scheme 18). To a solution of aminopentanol 113 (3.1g, 30 mmol) and triethylamine (TEA) (4.2 ml, 3.03g, 30 mmol) in 50 ml of anhydrous THF was added dropwise *p*-toluenesulfonyl chloride 115 (5.7g, 30 mmol) in 50 ml of THF at 0 °C. The resulting solution was continued to stir at 0 °C and then rt for 2 h. To the reaction solution was added 500 ml of water and the resulted mixture was extracted

with EtOAc. The combined organic phase was washed with water twice, 0.5 N HCl solution once, 5% NaHCO<sub>3</sub> solution once and water once. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under high vacuum to give 4.87g (63%) of the compound 116 as a white oil. The compound was used to prepare compound 118  
5 without further purification; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.33-1.37 (m, 2H), 1.45-1.51 (m, 4H), 2.41 (s, 3H), 2.91 (t, 2H), 3.57 (t, 2H), 7.30 (d, 2H), 7.72 (d, 2H); MS (ESI) *m/z* 280.5 (M + Na)<sup>+</sup> (C<sub>12</sub>H<sub>19</sub>NO<sub>3</sub>SNa requires 280.4).

Compound 118 (Scheme 18). To a solution of compound 116 (1.29g, 5mmol), naproxen 1 (1.15g, 5 mmol) and DMAP (0.12g, 1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> was  
10 added DCC (1.03g, 5 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 2h and then at rt for another 2 h. The solid was filtered off and the solvent was evaporated. The residue was dissolved in EtOAc and filtered to remove more solid. The filtrate was washed with water three times, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The product was purified by flash chromatography on a silica gel column using ethyl ether  
15 as an eluent to give 2.06g (88%) of the compound 118 as a solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.13-1.18 (m, 2H), 1.25-1.34 (m, 2H), 1.45-1.51 (m, 2H), 1.55 (d, 3H), 2.40 (s, 3H), 2.77 (q, 2H), 3.81 (q, 1H), 3.90 (s, 3H), 3.96-4.02 (m, 2H), 4.47 (t, 1H, ex D<sub>2</sub>O), 7.12-7.14 (m, 2H), 7.26 (d, 2H), 7.38 (d, 1H), 7.65-7.70 (m, 5H); MS (ESI) *m/z* 492.5 (M + Na)<sup>+</sup> (C<sub>26</sub>H<sub>31</sub>NO<sub>5</sub>SNa requires 492.6).

20

#### Example 49

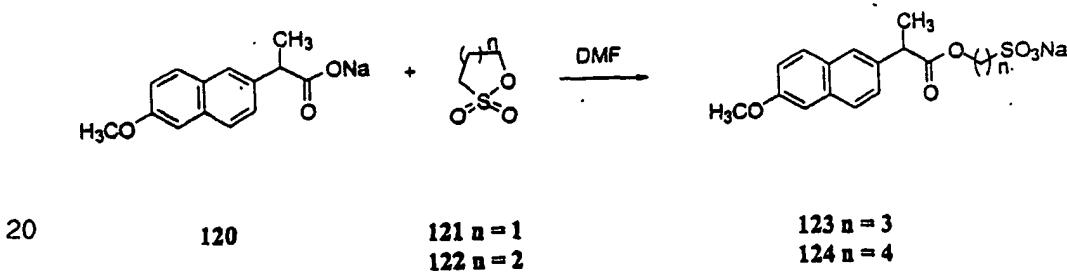
Compound 117 (Scheme 18). Compound 117 was prepared by the similar procedure as described above for compound 116 from 6-amino-1-hexanol 114 (3.5g, 30 mmol) and compound 115 (5.7g, 30 mmol). The product was purified by flash  
25 chromatography on a silica gel column using ethyl ether as an eluent to give 6.5g (80%) of the compound 117 as a white solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.26-1.29 (m, 4H), 1.43-1.49 (m, 4H), 2.40 (s, 3H), 2.89 (t, 2H), 3.57 (t, 2H), 7.27 (d, 2H), 7.73 (d, 2H); MS (ESI) *m/z* 272.4 (M + H)<sup>+</sup> (C<sub>13</sub>H<sub>22</sub>NO<sub>3</sub>S requires 272.4).

**Compound 119 (Scheme 18).** Compound 119 was prepared by the similar procedure as described above for compound 118 from compound 117 (1.36g, 5 mmol), naproxen 1 (1.15g, 5 mmol), DCC (1.03g, 5 mmol) and DMAP (0.12g, 1 mmol). The product was purified by flash chromatography on a silica gel column using ethyl ether as an eluent to give 2.04g (84%) of the compound 119 as a white solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.11 (m, 4H), 1.23-1.29 (m, 2H), 1.46-1.56 (m, 2H), 1.56 (d, 3H), 2.40 (s, 3H), 2.79 (q, 2H), 3.82 (q, 1H), 3.91 (s, 3H), 3.96-4.05 (m, 2H), 4.43 (t, 1H, ex D<sub>2</sub>O), 7.11-7.14 (m, 2H), 7.26-7.29 (m, 2H), 7.37-7.39 (q, 1H), 7.64-7.72 (m, 5H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 18.5, 21.7, 25.4, 26.1, 28.4, 29.5, 43.1, 45.7, 55.5, 64.6, 105.8, 119.1, 126.1, 126.4, 127.3, 129.1, 129.4, 129.8, 133.8, 136.1, 137.2, 143.5, 157.8, 174.1; MS (ESI) *m/z* 484.7 (M + H)<sup>+</sup> (C<sub>27</sub>H<sub>34</sub>NO<sub>5</sub>S requires 484.6).

The syntheses described in Examples 50 and 51 are outlined in Scheme 19.

**Scheme 19**

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**Example 50**

**Compound 123 (Scheme 19).** A mixture of naproxen sodium 120 (2.52g, 10 mmol) and propanesultone 121 (1.22g, 10 mmol) in 50 ml of *N,N*-dimethylformamide (DMF) was stirred at 50-60 °C for 30 min. To the reaction solution was added 150 ml of acetone and then stood still for 1 h. Filtration and washing by acetone provided 3.2g (86%) of the compound 123 as a white powder; <sup>1</sup>H NMR (D<sub>2</sub>O) δ 1.37 (d, 3H), 1.93-1.97 (m, 2H), 2.74-2.77 (m, 2H), 3.72 (q, 1H), 3.72 (s, 3H), 4.01-4.05 (m, 1H), 4.08-4.11 (m, 1H), 6.97-7.00 (m, 2H), 7.20-7.22 (q, 1H), 7.44 (s, 1H), 7.50 (t, 2H); <sup>13</sup>C NMR (D<sub>2</sub>O) δ 16.7, 23.1, 44.4, 46.9, 54.6, 63.2, 105.4, 117.9, 125.1, 125.5,

126.7, 128.1, 128.7, 132.7, 134.9, 156.3, 176.4; MS (ESI) *m/z* 397.1 (M + Na)<sup>+</sup> (C<sub>17</sub>H<sub>19</sub>Na<sub>2</sub>O<sub>5</sub>S requires 397.4).

#### Example 51

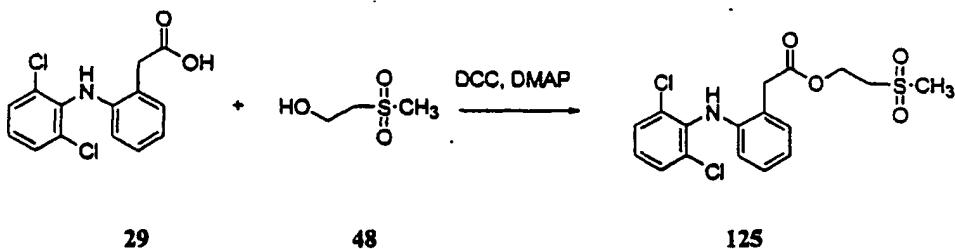
**Compound 124** (Scheme 19). Compound 124 was prepared by the similar procedure as described above for compound 123 from butanesulton 122 (1.02 ml, 1.36g, 10 mmol) and naproxen sodium 120 (2.52g, 10 mmol). After reaction, acetone was added and the solid was filtered and washed with acetone to give 1.3 g (34%) of the compound 124 as a white powder; <sup>1</sup>H NMR (D<sub>2</sub>O) δ 1.22 (d, 3H), 1.34-1.38 (m, 2H), 1.50-1.56 (m, 2H), 2.65 (t, 2H), 3.44 (s, 3H), 3.47 (m, 1H), 3.74-3.77 (m, 1H), 10 3.83-3.86 (m, 1H), 6.74 (s, 1H), 6.78-6.81 (d, 1H), 7.05 (d, 1H), 7.22-7.29 (m, 3H); MS (ESI) *m/z* 411.2 (M + Na)<sup>+</sup> (C<sub>18</sub>H<sub>21</sub>Na<sub>2</sub>O<sub>6</sub>S requires 411.2).

The synthesis described in Example 52 is outlined in Scheme 20.

#### Scheme 20

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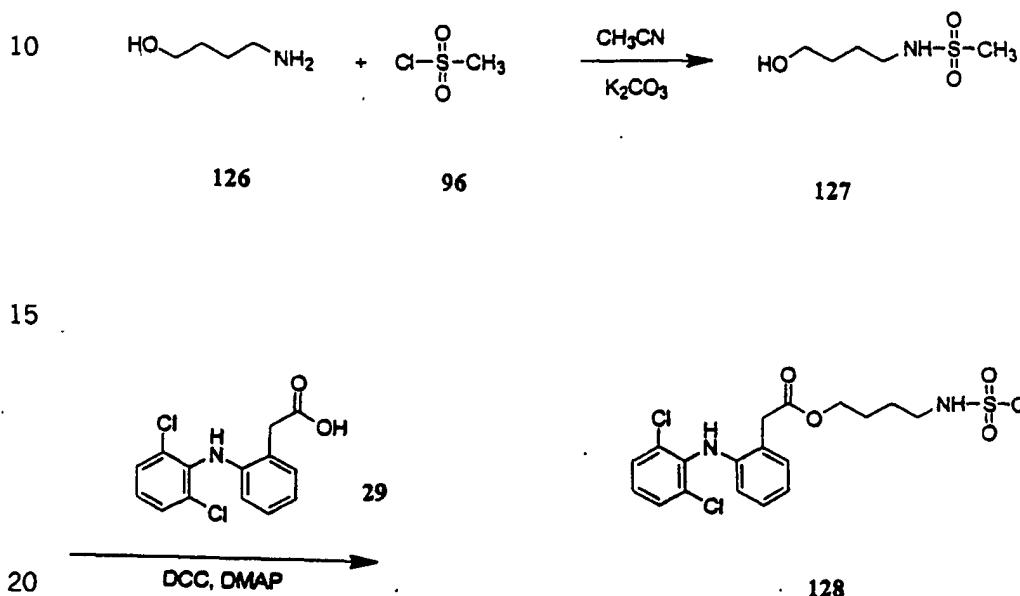
#### Example 52

**Compound 125** (Scheme 20). To a mixture of diclofenac 29 (2.96g, 10 mmol), methylsulfonylethanol 48 (1.24g, 10 mmol) and DMAP (0.24g, 2 mmol) in 50 ml of CH<sub>2</sub>Cl<sub>2</sub> was added DCC (2.06g, 10 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 2 h. The mixture was filtered and the filtrate was evaporated. The residue was washed with methanol to give 1.83g (92%) of the compound 125 as a white powder; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.75 (s, 3H), 3.30 (t, 2H), 3.84 (s, 2H), 4.58 (t, 2H), 6.51 (d, 1H), 6.93 (t, 1H), 7.00 (t, 1H), 7.12 (t, 1H), 7.19 (d, 1H), 7.34 (d, 2H); 30 <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 38.5, 42.1, 54.0, 58.8, 118.3, 122.2, 123.4, 124.7, 128.6, 129.1,

129.9, 131.1, 137.6, 142.8, 171.5; MS (ESI)  $m/z$  402.4 M<sup>+</sup> (C<sub>17</sub>H<sub>17</sub>Cl<sub>2</sub>NO<sub>4</sub>S requires 402.4).

The synthesis described in Example 53 is outlined in Scheme 21.

## 5 Scheme 21



### Example 53

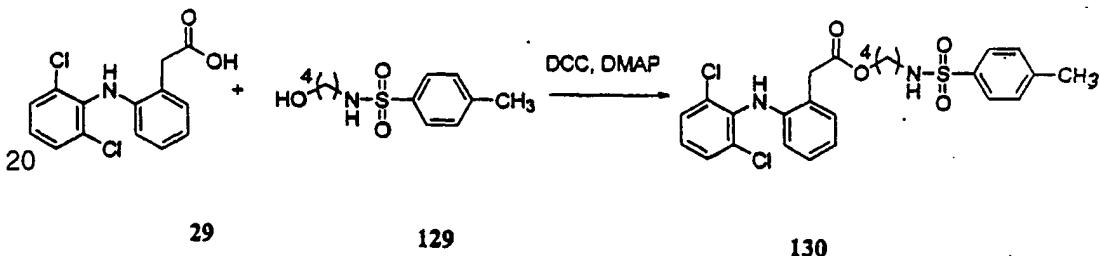
**Compound 127 (Scheme 21).** To a mixture of 4-amino-1-butanol **126** (9g, 100 mmol) and  $\text{K}_2\text{CO}_3$  (34.5g, 250 mmol, 2.5 equiv) in 200 ml of acetonitril was added dropwise methanesulfonyl chloride **96** (6.95 ml, 10.3g, 90 mmol, 3 equiv) in 100 ml of  $\text{CH}_3\text{CN}$  at 0 °C. The resulting solution was stirred at 0 °C for 1 h. The reaction mixture was filtered and the solvent was evaporated. The residue was purified by flash chromatography on a silica gel column using 50:1  $\text{CH}_2\text{Cl}_2$ -MeOH as an eluent to give 3.45g (21%) of the compound **127** as a white powder;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.42-1.49 (m, 4H), 2.89 (s, 3H), 2.91 (q, 2H), 3.39 (q, 2H), 4.39 (t, 2H),

6.91 (t, 1H, ex D<sub>2</sub>O); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 26.1, 29.6, 42.4, 60.2, one peak is covered by DMSO-d<sub>6</sub> peaks; MS (ESI) *m/z* 190.1 (M + Na)<sup>+</sup> (C<sub>5</sub>H<sub>13</sub>NO<sub>3</sub>SNa requires 190.2).

**Compound 128** (Scheme 21). Compound 128 was prepared by the similar procedure as described above for the compound 125 from diclofenac 29 (1.48g, 5 mmol), compound 127 (0.83g, 5 mmol), DCC (1.03g, 5 mmol) and DMAP (0.12g, 1 mmol). The product was purified by recrystallization from CH<sub>2</sub>Cl<sub>2</sub>-hexanes to give 1.5g (67%) of the compound 128 as a white powder; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.57-1.62 (m, 2H), 1.70-1.74 (m, 2H), 2.91 (s, 3H), 3.11 (q, 2H), 3.80 (s, 2H), 4.17 (t, 2H), 4.44 (t, 1H, ex D<sub>2</sub>O), 6.54 (d, 1H), 6.87 (bs, 1H, ex D<sub>2</sub>O), 6.94-7.00 (m, 2H), 7.12 (t, 1H), 7.23 (t, 1H), 7.34 (d, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 25.8, 26.8, 38.8, 40.5, 42.9, 64.7, 118.4, 122.2, 124.3, 124.4, 128.2, 129.1, 129.7, 131.1, 137.9, 142.9, 172.5; MS (ESI) *m/z* 445.3 M<sup>+</sup> (C<sub>19</sub>H<sub>22</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S requires 445.3).

15 The synthesis described in Example 54 is outlined in Scheme 22.

**Scheme 22**



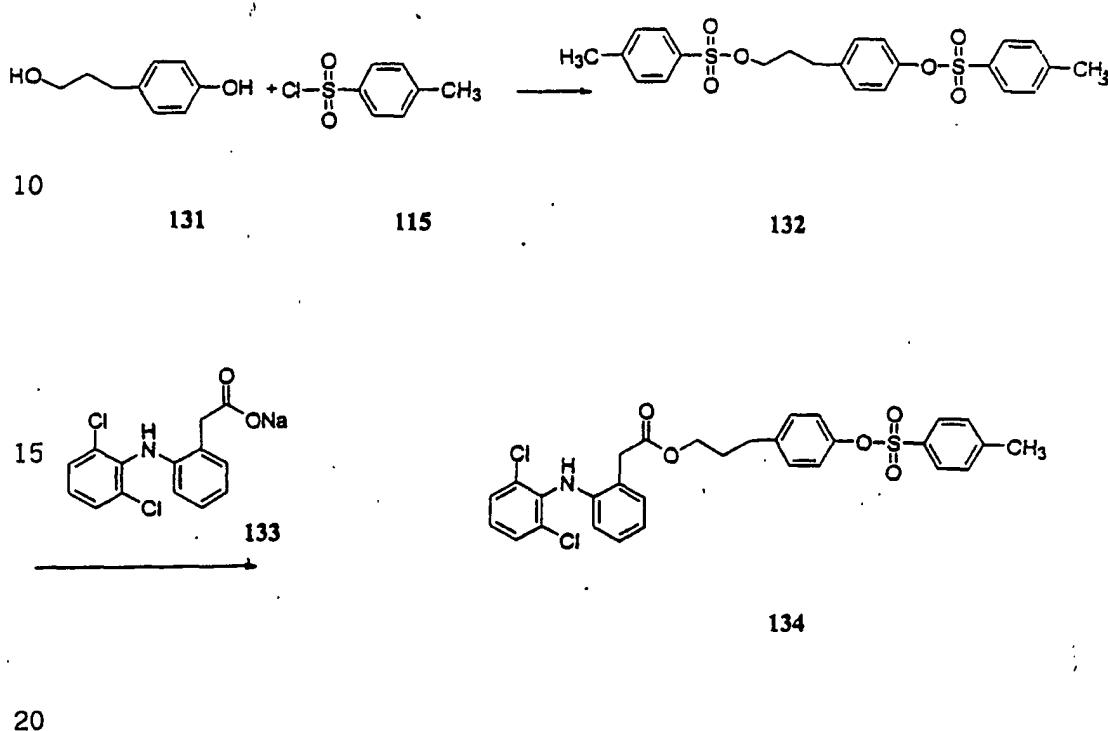
**Example 54**

25 **Compound 130** (Scheme 22). Compound 130 was prepared by the similar procedure as described above for the compound 125 from diclofenac 29 (1.48g, 5 mmol), compound 129 (1.22g, 5 mmol), DCC (1.03g, 5 mmol) and DMAP (0.12g, 1 mmol). The product was purified by recrystallization from CH<sub>2</sub>Cl<sub>2</sub>-hexanes to give 1.3g (50%) of the compound 130 as a white powder; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.47-1.51 (m, 2H), 1.62-1.66 (m, 2H), 2.41 (s, 3H), 2.90-2.94 (q, 2H), 3.77 (s, 2H), 4.09(t, 2H),

4.34 (t, 1H, ex D<sub>2</sub>O), 6.53 (d, 1H), 6.86 (bs, 1H, ex D<sub>2</sub>O), 6.93-7.00 (m, 2H), 7.11 (m, 1H), 7.20 (d, 1H), 7.28-7.35 (m, 4H), 7.72 (d, 2H); MS (ESI) *m/z* 544.2 (M + Na)<sup>+</sup> (C<sub>21</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>4</sub>SNa requires 544.4).

The synthesis described in Example 55 is outlined in Scheme 23.

## 5 Scheme 23



### Example 55

**Compound 132** (Scheme 23). To a solution of 4-(hydroxyphenyl)-1-propanol 131 (3.04g, 20 mmol) in 20 ml of pyridine was added compound 115 (15.2g, 80 mmol, 4 equiv) at 0 °C. The resulting solution was stirred at 0 °C for 2 h and then at rt for another 2 h. To the reaction solution was added 200 ml of water. The resulting mixture was extracted with EtOAc twice. The combined organic phase was washed with water five times, 0.5N HCl solution once, 5%  $\text{Na}_2\text{CO}_3$  solution once and water again. The organic phase was dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was evaporated to give 7.9g (86%) of the compound 132 as a pale yellow oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.90 (m,

2H), 2.4 (s, 6H), 2.6 (t, 2H), 3.98 (t, 2H), 6.82-6.84 (q, 2H), 6.97 (d, 2H), 7.29-7.34 (q, 4H), 7.68 (d, 2H), 7.76 (d, 2H); MS (ESI)  $m/z$  483.3 ( $M + Na$ )<sup>+</sup> ( $C_{23}H_{24}O_4S_2Na$  requires 483.5).

5           **Compound 134** (Scheme 23). A mixture of diclofenac sodium 133 (1.59g, 5 mmol), compound 132 (2.3g, 5 mmol) and  $K_2CO_3$  (1.38g, 10 mmol) was stirred at rt for 22 h. After reaction, water and EtOAc were added and the two layers were separated. The organic phase was washed with water four times, dried ( $Na_2SO_4$ ) and concentrated. The residue was purified by flash chromatography on a silica gel 10 column using 5:1  $CH_2Cl_2$ -hexanes as an eluent to give 1.7g (59%) of the compound 134 as a pale yellow oil;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.90-1.96 (m, 2H), 2.43 (s, 3H), 2.60 (t, 2H), 3.79 (s, 3H), 4.12 (t, 2H), 6.55 (d, 1H), 6.87 (t, 3H), 6.94-7.01 (m, 4H), 7.09-7.13 (m, 1H), 7.22-7.35 (m, 5H), 7.69 (d, 2H);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  22.1, 30.4, 31.8, 32.5, 64.8, 118.7, 122.5, 122.7, 124.5, 124.8, 128.5, 128.9, 129.3, 129.9, 129.95, 130.1, 131.2, 132.9, 138.2, 140.5, 143.1, 145.7, 148.4, 172.7; MS (ESI)  $m/z$  584.3  $M^+$  ( $C_{30}H_{27}Cl_2NO_5S$  requires 584.5<sup>1</sup>):

#### Example 56

Reduced numbers of intestinal ulcers in rat acute and subacute enteropathy models by 20 the invention modified NSAID (compound 19), a prodrug of naproxen

NSAIDs are important drugs used to treat acute and chronic inflammation as well as pain and fever. The major limitation to NSAID use is the occurrence of 25 gastrointestinal ulcers and erosions. These side effects are produced by a combination of local and systemic effects. Attempts have been made to circumvent the local side effects of NSAIDs by making them as prodrugs, which will bypass the stomach, but so far this has not been clearly successful. It is demonstrated here that the invention modified NSAIDs substantially reduce GI toxicity, while exhibiting dose equivalent

efficacy in anti-inflammation activity in both acute and chronic inflammation animal models.

5 Sprague-Dawley rats (male, 150 - 200 g), were orally dosed once daily for either 3 days (acute model) or 14 days (subacute model). Twenty-four hours after the last dose, the rats were injected i.v. with Evans Blue (5 ml/kg, 10 mg/ml) to stain the 10 ulcers. Ten to twenty minutes later the animals were sacrificed by CO<sub>2</sub> inhalation and the intestines removed, opened lengthwise and the contents removed. The long dimensions of all ulcers were measured using a ruler and summed to give a total ulcer score.

15 In the acute model (Figure 1), ulceration after dosing with an invention modified NSAID (compound 19) was 15% of that seen with an equimolar dose of naproxen. PEG had no ulcerogenic effect. In the subacute model (Figure 2), ulceration was less than 5% of that seen with a corresponding dose of naproxen at all three doses used. Again, PEG had no effect. These results suggest that invention modified NSAIDs are much less ulcerogenic than naproxen.

#### Example 57

20 Reduction of chronic hindlimb inflammation in the rat adjuvant arthritis model by the invention modified NSAID (compound 19), a prodrug of naproxen

25 NSAIDs are useful in the treatment of both chronic and acute inflammatory conditions. Efficacy in chronic inflammation can be estimated using the rat adjuvant arthritis model. In this model Lewis male rats (175-250 g) are injected intradermally in the footpad with *M. tuberculosis* powder suspended in mineral oil at 5 mg/ml. Progressive swelling of the uninjected paw and ankle joint between days 5 and 15 is measured by plethysmometry.

Rats were dosed daily by oral gavage with 5 ml/kg of naproxen at 3 to 30 mg/kg in phosphate buffered saline (PBS) and with equimolar doses of an invention modified NSAID at 1 ml/kg in PEG 300. The results (Figure 3) show that the invention modified NSAID resulted in antiinflammatory effects comparable to those 5 of naproxen in this model.

#### Example 58

Reduction of acute hindlimb inflammation in the rat carrageenan-induced hindlimb edema model by the invention modified NSAID (compound 19), a prodrug of  
10 naproxen

Efficacy of NSAIDs in acute inflammation can be estimated by using intraplantar injection of carrageenan in the rat. Sprague-Dawley rats (200-250 g male) are injected intradermally in the footpad with 50 (1 of a 1% carrageenan solution in 15 PBS. Swelling of the injected paw is measured 3 & 4 hours later, using a plethysmometer.

Pretreatment with oral naproxen one hour before the carrageenan injection at 10 mg/kg resulted in an approximately 50% reduction in swelling at both time points 20 (Table 1). An equimolar dose of an invention modified NSAID reduced inflammation to the same degree at both time points. These results suggest that invention modified NSAIDs are comparable in effect to naproxen at 10 mg/kg.

**Table 1.** Effects of naproxen and the invention modified NSAID (compound 19) on paw volume increase in carrageenan-induced inflammation in rats.

Treatment	4 Hours	5 Hours
Vehicle	0.73 $\pm$ 0.10	0.85 $\pm$ 0.10
Naproxen (1 mg/kg)	0.63 $\pm$ 0.07	0.75 $\pm$ 0.08
Naproxen (10 mg/kg)	0.32 $\pm$ 0.05*	0.39 $\pm$ 0.07*
Compound 19 (1.75 mg/kg)	0.78 $\pm$ 0.04	0.93 $\pm$ 0.04
Compound 19 (17.5 mg/kg)	0.34 $\pm$ 0.06*	0.40 $\pm$ 0.06*

P < 0.05 vs Vehicle by unpaired t-test.

5

Invention modified NSAIDs are seen to have antiinflammatory activity similar to naproxen in the chronic adjuvant arthritis and acute carrageenan hindlimb edema rat models. The tendency to cause intestinal ulcers is reduced substantially invention modified NSAID. Thus, invention modified NSAIDs provide an effective prodrug 10 form of naproxen with reduced intestinal side effects.

#### Example 59

Plasma pharmacokinetics of naproxen and the invention modified NSAID after oral administration in rats

15

The invention compound (compound 19) is a naproxen prodrug, which is a conjugate of naproxen and tosylate. Oral administration of the invention compound resulted in the release of free naproxen. The pharmacokinetics of naproxen release from the invention modified NSAID and its parent drug, naproxen, was evaluated in 20 rats after oral administration.

The carotid artery of Sprague-Dawley rat (250-350 g, male) was catheterized at least one day before drug administration and flushed with 30% polyvinyl pyrrolidone (PVP) (400 U/mL of heparin) to maintain patency. At predetermined

time points (see Table 2), blood samples (250 (L) were collected by unhooking the flushing syringe and letting the blood flow out of the catheter and into the centrifuge tubes. After centrifugation (13,000 rpm, 10 min, 4oC), the plasma samples were collected and analyzed in the same day.

5

**Table 2.** Rat group assignment and doses

Test Article	Group #	Rat #	Dose* (mg/kg)	Sample Time
Naproxen	1	1, 2, 3, & 4	Oral (2 mg/kg)	5 min, 0.5, 1, 4, 7, 10, 13, 16, 19, 22, & 24 hrs
Invention Compound 19	2	5, 6, 7, & 8	Oral (2 mg/kg)	15 min, 0.5, 1, 3, 5, 6, 7, 8, 22, 23, & 24 hrs

\*Indicates amount of naproxen in dose.

Aliquot of plasma sample (100  $\mu$ L) was mixed with 200  $\mu$ L of acetonitrile.

10 After vortexing and centrifugation (13,000 rpm, 10 min, 4°C), 200 (L of supernatant was removed and added to 300 (L of a 58:42 mixture of 50 mM phosphate buffer (pH 5.0) and acetonitrile. Following vortexing and centrifugation, 25 L of supernatant was removed and analyzed by HPLC with a UV detection system.

15 The average plasma concentration at each time point was calculated and utilized in a pharmacokinetic analysis. Noncompartmental pharmacokinetic analysis was carried out using WinNolin (Pharsight, Mountainview, California) to calculate the maximum concentration ( $C_{max}$ ), time to maximum concentration ( $T_{max}$ ), area under the curve from zero to the last time point ( $AUC_{last}$ ), the area under the curve from zero to 20 infinite time ( $AUC_{inf}$ ), and the terminal phase half life ( $Beta-t_{1/2}$ ).

25 The  $AUC_{all}$ ,  $AUC_{INF}$ , and  $t_{1/2}$  of naproxen from naproxen and a modified form of naproxen according to the invention were found to be similar (Table 3). On the other hand, for the invention modified form of naproxen, the  $C_{max}$  was lower and the  $T_{max}$  longer, compared to naproxen (see Table 3).

other hand, for the invention modified form of naproxen, the  $C_{max}$  was lower and the  $T_{max}$  longer, compared to naproxen (see Table 3).

5 **Table 3 - Non-Compartmental Pharmacokinetic Analysis of naproxen and the invention modified form of naproxen according to the (compound 19) after oral administration in rats**

Drug	Dose* (mg/kg)	$C_{max}$ ( $\mu$ g/mL)	$T_{max}$ (hrs)	$AUC_{all}$ ( $\mu$ g*hr/mL)	$AUC_{INF}$ ( $\mu$ g*hr/mL)	$t_{1/2}$ (hrs)	N
Naproxen	2	7.77 $\pm$ 4.13	0.5 $\pm$ 0.5	50 $\pm$ 6	55 $\pm$ 7	6.2 $\pm$ 0.4	4
Invention modified naproxen	2	3.87 $\pm$ 1.05	6.8 $\pm$ 1.5	49 $\pm$ 10	56 $\pm$ 14	6.8 $\pm$ 2.7	4

\*Indicates amount of naproxen in dose.

10 Following oral naproxen administration, the naproxen plasma levels were at the highest at the first time-point (5 minutes) then declined in a bi-exponential manner. In contrast, after oral administration of a modified form of naproxen according to the invention, the maximum naproxen levels were observed at a much later time ( $T_{max}$  of 6.8 $\pm$ 1.5 hrs). The similar  $AUC_{all}$ ,  $AUC_{INF}$ , and  $t_{1/2}$  values but lower 15  $C_{max}$  and longer  $T_{max}$  values supports the conclusions drawn from the results obtained from pharmacological studies, i.e. that a modified form of naproxen according to the invention conjugate has equivalent pharmacological efficacy and greatly improved gastrointestinal safety profile compared to naproxen.

20 While the invention has been described in detail with reference to certain preferred embodiments thereof, it will be understood that modifications and variations are within the spirit and scope of that which is described and claimed.

## WHAT IS CLAIMED IS:

1. A compound having the structure:

5

X-L-Z

wherein:

X = a non-steroidal anti-inflammatory drug (NSAID),

10 L = an optional linker/spacer,

Z = a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety.

2. A compound according to claim 1 wherein said NSAID is

15 acetaminophen, aspirin, ibuprofen, choline magnesium salicylate, choline salicylate, diclofenac, diflunisal, etodolac, fenoprofen calcium, flurobiprofen, indomethacin, ketoprofen, carprofen, indoprofen, ketorolac tromethamine, magnesium salicylate, meclofenamate sodium, mefenamic acid, oxaprozin, piroxicam, sodium salicylate, sulindac, tolmetin, meloxicam, nabumetone, naproxen, lornoxicam, nimesulide, 20 indoprofen, remifentanil, salsalate, tiaprofenic acid, or flosulide.

3. A compound according to claim 2 wherein said NSAID is naproxen, aspirin, ibuprofen, flurbiprofen, indomethacin, ketoprofen, or carprofen.

25 4. A compound according to claim 1 wherein the sulfur-containing functional group is sulfonate, reverse sulfonate, sulfonamide, reverse sulfonamide, sulfone, sulfinate, or reverse sulfinate.

30 5. A compound according to claim 4 wherein the sulfur-containing functional group is sulfonate or reverse sulfonate.

6. A compound according to claim 5 wherein the sulfur-containing functional group is an optionally substituted aromatic sulfonate.

5

7. A compound according to claim 6 wherein said aromatic sulfonate is tosylate or brosylate.

10 8. A compound according to claim 5 wherein the sulfur-containing functional group is an optionally substituted C1 to C10 alkyl sulfonate.

9. A compound according to claim 8 wherein the alkyl sulfonate is mesylate or triflate.

15 10. A compound according to claim 4 wherein the sulfur-containing functional group is a sulfone.

11. A compound according to claim 10 wherein the sulfur-containing functional group is an optionally substituted C<sub>1</sub> to C<sub>10</sub> alkyl sulfone.

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12. A compound according to claim 11 wherein said sulfone is methyl sulfone, ethyl sulfone.

25 13. A compound according to claim 10 wherein the sulfur-containing functional group is an optionally substituted aromatic sulfone.

14. A compound according to claim 13 wherein the sulfur-containing functional group is a p-substituted aromatic sulfone.

15. A compound according to claim 4 wherein the sulfur-containing functional group is a sulfonamide or reverse sulfonamide.

16. A compound according to claim 15 wherein the sulfur-containing 5 functional group is an optionally substituted C<sub>1</sub> to C<sub>10</sub> alkyl sulfonamide.

17. A compound according to claim 16 wherein the sulfur-containing functional group is methyl sulfonamide.

10 18. A compound according to claim 15 wherein the sulfur-containing functional group is an optionally substituted aromatic sulfonamide.

19. A compound according to claim 18 wherein the sulfur-containing functional group is toluene sulfonamide.

15 20. A compound according to claim 4 wherein the sulfur-containing functional group is a sulfinate or reverse sulfinate.

21. A compound according to claim 1 wherein L, when present, has the 20 structure:

W-R-

wherein:

25 R is optional, and when present is alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, heterocyclic, substituted heterocyclic, oxyalkylene, substituted oxyalkylene, alkenylene, substituted alkenylene, arylene, substituted arylene, alkarylene, substituted alkarylene, aralkylene or substituted aralkylene, and

W is ester, reverse ester, thioester, reverse thioester, amide, reverse amide, phosphate, phosphonate, imine or enamine.

22. A formulation comprising a compound according to claim 1 in a pharmaceutically acceptable carrier therefor.

23. A formulation according to claim 22 wherein said pharmaceutically acceptable carrier is a solid, solution, emulsion, dispersion, micelle or liposome.

24. A formulation according to claim 22 wherein said pharmaceutically acceptable carrier further comprises an enteric coating.

10 25. A method for the alleviation of side effects induced by the administration of a non-steroidal anti-inflammatory drug (NSAID) to a subject, said method comprising chemically modifying said NSAID prior to administration to a subject, wherein said NSAID is chemically modified so as to

15 a) reduce the maximum concentration ( $C_{max}$ ) relative to the unmodified NSAID and  
b) maintain a therapeutically effective concentration of said NSAID in plasma upon administration to said subject.

20 26. The method according to claim 25, wherein the  $C_{max}$  is reduced relative to the unmodified NSAID by about 10% to 90 %.

27. The method according to claim 26, wherein the  $C_{max}$  is reduced relative to the unmodified NSAID by about 20% to 80 %.

25 28. The method according to claim 27, wherein the  $C_{max}$  is reduced relative to the unmodified NSAID by about 40% to 70 %.

29. The method according to claim 25, wherein the NSAID is chemically modified so as to achieve a  $C_{max}$  upon administration at or below the  $IC_{50}$  value for COX 30 1 enzyme.